REMARKS

Claims 44-52 are active in the case. Election of Group II, claims 32-43, is affirmed. Non-elected Claims 1-31 have been canceled without prejudice or disclaimer.

Support for the Amendments

Method claims 32-43 have been canceled and rewritten as claims 44 – 52.

Claim 44 is supported as follows: a method for treating osteoporosis in a mammal, by administering an effective amount of an effervescent bisphosphonate composition (page 5, ¶17) containing a bisphosponate, an acid component and an alkaline effervescing component (page 4, ¶13); with a solid composition weight of about 3,500 mg to about 6,000 mg (page 13, ¶45);

an acid component selected from citric acid, tartaric acid and alkali metal salts thereof (page 7, lines 1-3);

an acid component content of about 45 – 60 wt.% (page 8, ¶30, line 2 and page 11, ¶37, line 5),

an alkaline component selected from alkali metal carbonates and bicarbonates (page 7, ¶27); with alkaline component content of about 30 – 55 wt.% (page 11, ¶37, line 10),

an effervescent solution having buffered pH of 4.5 to about 5.5 (page 7, ¶28, lines 14-17; page 14, lines 1-2 (pH is raised to not above about 6).

Claim 45 is supported by original claim 11.

Claim 46 is supported by ¶30, line 2 (acid component 45 - 60%).

Claim 47: page 12, ¶40 (tablet).

Claim 48: page 13, ¶45 (total weight of about 5,000 mg).

Claim 49: page 9, ¶34 (solublizing agent), page 10, ¶35 (sweetener).

Claim 50: page 9–10, ¶34 (specific solublizing agents).

Claim 51: original claim 14, and page 8, line 9 (mediate the patients stomach pH for at least 15 minutes).

Claim 52: page 6, ¶24, lines 9–11 (bisphosphonate dose)

35 USC 112, 1st paragraph

Claims 32-43 are rejected under 35 USC 112, 1st paragraph, on enablement grounds. The rejected claims have been replaced by claims 44-52, which recite specific acid and alkaline components disclosed in the specification. The Examiner's remarks acknowledged that citrate/carbonate/bicarbonate systems are enabled by the specification (see Official Action page 5, lines 5-7). As now presented, no undue experimentation would be required to practice the claimed invention.

Rejections over Prior Art

The present invention relates to an osteoporosis treatment using effervescent bisphosphonate compositions having a selected pH of 45 to about 5.5, and very high buffering capacity, which serves two purposes: 1) to mediate the stomach pH, and 2) to cause the stomach to rapidly eject the effervescent solution.

The applicants have recognized that a buffered, low pH environment inhibits acid rebound (the natural process of acid secretion that occurs whenever food enters the stomach), and that a large quantity of the buffer system (3.5 grams or more total weight) causes the stomach to eject the effervescent solution quickly. This combination reduces the esophageal irritation often seen with bisphosphonates. (Hayward Declaration ¶7 submitted herewith)

All patients now on conventional bisphosphonate treatments are instructed to remain upright for at least 30 minutes after each dose. Even so, they often cannot tolerate these drugs

due to irritation of the esophagus and gastric lining. (Hayward Declaration¶5) Although administration of bisphosphonates in liquid form is known - including in effervescent liquid - the improved dosage system of the present invention has not been recognized before.

Claims 32-35 are rejected under 35 USC 102(b) as being anticipated by Katdare et al. (US 5,853,759).

Katdare et al. teaches generically that bisphosphonates can be administered in effervescent solution. The Examiner has calculated that such formulations should have a pH range of about 3 to 6.5, based on the known pKa values of citric acid. The applicants have shown by experiment that that estimate is correct. Examples 1-4 of Katdare et al. have pH values of 4.3, 6.4, 6.1 and 6.7, respectively. This data shows, however, that the Katdare et al. examples are all outside the claimed pH range of 4.5 to about 5.5. (Rohrich Declaration ¶6 submitted herewith).

Most importantly, Katdare et al. did not recognize that it isn't enough to merely dissolve the bisphosphonate in an effervescent system. In addition, the pH should be selected to minimize acid rebound so that the buffering system can have enough capacity to mediate stomach pH and absorb any acid produced. Also, the relatively large amount of buffering reagents promotes rapid ejection of the effervescent solution from the stomach and so helps prevent gastric irritation. As amended, the claims recite compositions having a large amount of the buffering system (3.5 to about 6 grams total weight, with a relatively high minimum percentage of acid), at a specific pH range of 4.5 to about 5.5. This combination of pH and buffering capacity is not disclosed by Katdare et al., nor are the benefits of it suggested by the reference.

Table 1 of the Rohrich Declaration is reproduced below. It shows that the Katdare et al. examples typically have a pH of 6.1 or more. This high pH would be expected to promote acid

secretion by the stomach due to the acid rebound effect, and would not be optimal for administering bisphosphonates. (Hayward Declaration ¶9)

The pH of Katdare et al Example 1 was lower at 4.3, but its acid neutralizing capacity (ANC) is also very low, only 2.95 mEq of acid per dose. This is because it contains very little of the acid and alkaline components; just enough to dissolve the solids, but not enough to provide significant acid neutralizing capacity. ANC can be measured by titration with a pH meter, as described in USP Official Monographs (301) (Rohrich Declaration ¶4, and attachment).

One can compare this ANC = 2.95 mEq per dose with ordinary antacid tablets, which must have an ANC per dose of at least 5 mEq to even be considered antacids. (USP Official Monographs (302); Hayward Declaration ¶10 , and attachment.) While the USP antacid standard was developed specifically for calcium carbonate tablets, it does indicate that Example 1 of Katdare has very little buffering capacity. Thus it would not be expected to mediate the stomach pH significantly or provide much protection from irritation by the bisphosphonate compared to the present invention. (Hayward Declaration ¶10).

Finally, the Katdare et al. formulas all have very low total weights of about 1.1 - 2.5 grams, compared to 3.5 - 6 grams in the present invention. The small quantities of the effervescing system in Katdare et al. would not promote rapid ejection of the bubbling solution from the stomach, and so would be prone to cause more irritation for that reason as well. (Hayward Declaration ¶11).

In summary, Katdare et al. does not disclose the claimed compositions, and does not suggest increasing the amount of acid or alkaline components to provide high buffering capacity and effervescent action.

ANC of Test Formulations According to Patent Descriptions

	Invention				**US Patent 5,853,759** (Katdare et al.)				**US Patent 5,994,329**
	Example 2	Example 3	Example 4	Example 5	Example 1	Example 2	Example 3	Example 4	Example 8
Citric acid, mg	1400	420	525	475	650	590	530	600	56.3
Monosodium citrate, mg		1820	1820	1820					
Sodium bicarbonate, mg	800	800	800	800	367	850	850	1500	
Trisodiumcitrate dihydrate, mg									1500
Potassium bicarbonate, mg	694	695	695	695					
Sodium carbonate, mg	160	160	40	80	40	87		40	
Potassiumsodiumtartrate, mg		5	5	5					
Sorbitol, mg	446	450	615	625	47.5	35	190	392.5	
Total weight (dose)	3500	4350	4500	4500	1104.5	1562	1570	2532.5	1556.3
Start pH (dose in 70ml water)	5.7	5.7	5.4	5.5	4.3	6.4	6.1	6.7	6.75
ANC per dose (mEq)	12.6	17.6	14.9	15.7	2.95	9.7	7.8	16.1	6.9

Claims 32-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Daifotis et al. (US 5,994,329).

As now presented, the claims stand clear of the Daifotis et al. compositions. The examiner noted that Example 8 is a liquid bisphosphonate composition of pH 6.75 (column 19, lines 40-62). However, that liquid is not effervescent. It contains 1500 mg trisodiumcitrate dihydrate and 56.3 mg citric acid, but no effervescencing alkaline component. The ANC per dose is only 6.9 mEq in Example 8 (Rohrich Declaration, Table) due to the small quantity of buffering components. And without any carbonate or bicarbonate, the solution contains no bubbles and would not be ejected from the stomach as rapidly as the heavily effervescent and buffered solutions of the present invention. Accordingly, the rejection for anticipation under 35 U.S.C. 102(b) should be withdrawn.

Claims 40-43 are rejected under 35 U.S.C. 103(a) over Katdare et al. and Daifotis et al. in view of Samejima et al. (US 4,462,982).

The supporting reference, Samejima et al., was cited only to show that micro encapsulation of active agents is known for controlled release in the stomach (Official Action page 15, lines 5-18). However micro-encapsulation is not a limitation of the main claim, and so the following remarks will focus on whether the present invention would have been obvious in view of Katdare et al. and Daifotis et al.

Katdare et al. teaches that bisphosphonates can be administered in effervescent solution but, as discussed above, it does not suggest doing more than simply dissolving the drug in an effervescent liquid. It does not contemplate selecting the starting pH to minimize acid rebound, or providing a system with high buffering capacity effervescent action to promote rapid ejection

of the solution from the stomach. Nothing in Katedare et al. suggests a need for from 3.5 to about 6 grams total weight of solid components to achieve an effective buffering and bubbling system.

Daifotis et al. used a pH of 6.75, which is above the claimed range 4.5 to about 5.5; and its buffering capacity was only 6.9 mEq per dose (Rohrich Declaration, table), so Example 8 of Daifotis et al. is similar to Example 2 of Katdare et al. in terms of ANC per dose. Since the Daifotis solution is not effervescent, it would not have suggested increasing the amount of effervescent components in Katdare. Conversely, nothing in Katdare et al. would have motivated to a person of ordinary skill in the art to lower the pH of Daifotis et al. to about 5.5, or to increase the buffering capacity. There is no indication these changes would improve the administration of bisphosphonate drugs. Accordingly, the present invention would not have been obvious within the meaning of 35 U.S.C. 103(a).

CONCLUSION

Applicants submit respectfully that the present application is in condition for allowance.

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AUTHORIZATION

Applicants believe all fees due in connection with this filing are being paid herewith. However, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

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